

ABSTRACTS OF INVITED PRESENTATIONS

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The National Bioethics Advisory Commission's 'International Report': A New Generation of Challenges for International Research Ethics

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The assessment of the ethical acceptability of vaccine trials in developing countries is an issue both for U.S. sponsors and regulators and also for scientists, health policy bodies and ethics review bodies in host countries. The issue is complicated by the unique features and attendant risks of vaccine research, divergence of existing international guidelines on key issues, and by recent policy proposals in the United States, such as those in the National Bioethics Advisory Commission's (NBAC) Report on *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*.

NBAC's recommendations present an important challenge to conventional thinking about the ethics of international research. Despite their uncertain effect on U.S. policy some of the recommendations have found expression in other international guidelines and may reflect a sea-change in thinking about the role and obligations of investigators (and sponsors) in international collaborative research involving human subjects. As such, they represent an important way of thinking about what makes international research ethical.

This presentation will examine four of NBAC's key recommendations and their implications for international vaccine trials: (a) that research must be responsive to the health needs of the host country; (b) that investigators must meet the substantive requirements of informed consent; (c) that there must be prior agreements outlining the conditions of the trial, including post-trial obligations of the investigators/sponsors; and (d) that research activities must result in improved capacity within the host country. As well, these recommendations will be compared with key requirements of other relevant guidelines.

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Auto-Immunity Resulting from Bystander Immunological Effects

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T cells reactive with autoantigens are present in many normal individuals and there is little data to suggest that their frequency is greater in patients with autoimmune diseases than in normals. These autoreactive T cells do remain a potential reservoir of pathogenic effectors which when appropriately stimulated could precipitate an autoimmune state. As the induction and exacerbation of autoimmune diseases are associated with antecedent infectious illness, we have developed an animal model system to explore the potential role of microbial products in the conversion of these benign autoantigen-specific T cells into pathogenic effectors. The IL-12/IL-12 receptor pathway appears to play a critical role in this transformation. B10.S mice are resistant to the development of Experimental Allergic Encephalomyelitis (EAE) following immunization with myelin basic protein (MBP) in CFA. MBP-reactive T cells can be readily identified following immunization, but fail to produce IFN- γ when restimulated in vitro. However, following restimulation of these cells in the presence of antigen and microbial products (bacterial DNA, CpG oligonucleotides, LPS/IFN- γ), these T cells differentiated into pathogenic Th1 cells that produced IFN- γ and induced EAE in normal recipients. The ability of the microbial products to induce pathogenic autoreactive T cells was completely dependent on their capacity to induce IL-12 production. Thus, the production of IL-12 by cells of the innate immune system following stimulation by microbial products during the course of an infectious disease may facilitate the autoantigen-specific differentiation of autoimmune effector cells in the immediate microenvironment. These results are also compatible with the concept of molecular mimicry, as the induction of IL-12 by microbial products and the presence of cross-reactive determinants on the same pathogenic source could act synergistically to promote autoimmunity.

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The Significance of Immunological Mimicry for the Development of New Vaccination Strategies.

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Immunological or molecular mimicry has been proposed as a potential mechanism for initiation of autoimmune disease. We first proposed this almost 20 years ago when we showed that monoclonal antibodies that were specific for viral proteins also cross-reacted with host proteins. Later in searching databases for common epitopes between viruses and known host cell proteins, we found a cross-reactive T cell epitope between myelin basic protein (MBP) and the hepatitis B virus polymerase. This T cell cross-reactive epitope was the rabbit encephalitogenic epitope that could induce experimental allergic encephalomyelitis (EAE). We showed that: 1) when rabbits were sensitized with the cross-reactive viral peptide, autoantibodies to MBP were induced, 2) *in vitro* lymphoproliferative responses to MBP could be demonstrated and 3) an EAE-like disease in some of the rabbits occurred. This was the first demonstration that a viral peptide could induce autoimmunity through molecular mimicry. Noting our data, others have interpreted this to indicate that hepatitis B virus infection or inoculation of humans with the hepatitis vaccine could induce EAE or autoimmune central nervous system disease in humans. This is clearly not the case. First, we showed a cross-reaction between the rabbit EAE site and the viral polymerase. This does not cross-react with the human epitopes for EAE. Second, the hepatitis B virus polymerase is not contained in the recombinant vaccines on the market today. Third, the current adjuvant (Alum) used in vaccines favor a Th2-type immune response. CD4⁺ Th1 T cells mediate EAE.

Recently, we have made recombinant vaccinia viruses encoding self-CNS proteins. This is to determine whether infection with viruses having molecular mimicry with CNS proteins could modulate EAE. We found that infection of mice could either prime mice for EAE or protect from disease. Therefore, depending on the timing and antigen, different outcomes for autoimmunity will occur.

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INTEGRATED APPROACHES TO ASSESS AND LIMIT THE RISK OF AUTOIMMUNE ADVERSE EFFECTS

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Understanding how infections can occasionally induce autoimmune responses is key to our present assessment of a potential risk of autoimmune side effects associated with vaccination. It is known that, on the appropriate genetic background, microbial antigens which present epitopes mimicking autologous host epitopes may be recognized by the host immune system. At the B cell level, this is usually depending on the recognition of conformational epitopes. At the T cell level, small mimicking peptide sequences, if able to bind to the relevant MHC structure, can occasionally be seen by corresponding T cell receptors, provided such responsive T cells have escaped tolerogenic processes and do persist in the host T cell repertoire. Recent studies point out the degeneracy of the T cell recognition process and indicate that a functional mimicry can even occur, in extreme cases, in the absence of any shared amino acid between host and microbial peptides. However, induction of an autoimmune responses, like any immunological response, requires additional co-stimulatory signals. Furthermore, most autoimmune responses are not sufficient to cause a "real" disease in the absence of other facilitating pathogenic processes (e.g. local inflammation, genetic predisposition). These observations easily explain why the mere presence of potentially mimicking epitopes on vaccine antigens is not sufficient to imply a risk of autoimmune disease.

Another important infection-related mechanism which can be involved in the triggering of autoimmune manifestations, is related to non antigen-specific activation and maturation of dendritic cells (DC) as a result of triggering of toll-like receptors by microbial products or following viral infection by IL-12 inducing viruses. The DC activation and the associated release of high levels of pro-inflammatory cytokines may occasionally favour the activation or reactivation of an underlying silent autoimmune condition. For example, clinical studies have shown the profound impact of some acute respiratory infections, e.g. influenza, on the course of relapsing multiple sclerosis. Such effects have not been consistently observed with existing vaccines but some attention should probably be given to such potential side-effects in the development of new vaccine formulations which include potent Th1-driving adjuvants or newly attenuated viral strains.

So far, except for very rare instances (e.g. Guillain-Barré Syndrome, thrombocytopenia), vaccination has not been associated with autoimmune manifestations. However, special consideration may be given to the potential risk of autoimmune side-effects when dealing with the development of vaccines for infectious diseases known to be naturally associated with autoimmune manifestations (e.g. Group A Streptococcal disease or *Campylobacter jejuni* infection).

Therefore, although vaccination is unlikely to be a significant cause of AID, a comprehensive assessment of this risk at early development stage should help to reduce it to a minimal level.